REMARKS

A check for the fees for a three month extension of time and for filing the RCE is enclosed. Any fees that may be due with this paper or with this application during its entire pendency may be charged to Deposit Account No. 50-1213. If a Petition for Extension of Time is required, this paper is to be considered such Petition.

Claims 23 and 41-53 are pending in the application. Reconsideration of the withdrawal from consideration of claims 42 (in part), 43, 46 (in part), and 47 are respectfully requested as noted below. This application is filed in connection with a RCE; entry of the amendments and consideration of all pending claims are respectfully requested.

Claims 23, 42, 44, 46 and 48 are amended; and claims 50-53 are added. Claim 23 is amended. Particular basis for the amendment of claim 23 can be found, for example, in claim 23 as originally filed; at page 2, line 1, to page 3, line 9; page 5, lines 15-30; page 11, lines 9-19; page 12, lines 12-19; page 18, lines 20-26; page 30, lines 9-30; and page 13, lines 3-11 which begins as follows:

> 3-D structural models of the native protein or of the protein structural variants are then determined, either through experimental methods, for example, x-ray crystallography or NMR, from a protein structure database, such as the PDB, or by using any of a number of well known techniques for predicting protein structure from sequence, for example, homology modeling, *de novo* protein folding algorithms and methodologies, and other computational protein structure prediction methods. Homology modeling techniques are among those preferred herein.

In the amendment of claim 23 herein, the phrase "generating 3-D protein structural variant models from the sequences" is replaced with the phrase —determining 3-dimensional (3-D) protein structural variant models for the proteins that are the product of a gene exhibiting genetic polymorphisms— to render it clear that (1) the 3-D structures of the protein structural variant models

are determined and (2) the proteins whose structures are determined are the product of a gene exhibiting genetic polymorphisms.

It is respectfully submitted that, as discussed below, original claim 23 and amended claim 2, encompass a variety of methods, including, but not limited to, *ab initio* methods, for generating or determining 3-D protein structures. Original Claim 23, as filed and pending, is directed to a method of predicting clinical responses in patient that generate and employ 3-D structural models in the claimed methods. Thus, the amendment to claim 23 clarifies the language of the claim without altering the scope of original claim 23. Claim 23, as amended herein, is drawn to the same subject matter as originally elected claim 23. Claims 42, 44, 46, and 48 are amended to properly depend from claim 23. Claim 50 finds particular basis, for example, in original claim 23 and page 5, lines 15-30. Claims 51-53 find particular basis, for example, at pages 13-16. No new matter has been added.

RESTRICTION REQUIREMENT

The Examiner alleges that claims 42, 43, 46, and 47 are directed to subject matter that is independent or distinct from the originally claimed subject matter because claim 23 recites a step of "generating 3-D protein structural variant models from the sequences." In the Office action mailed August 13, 2002, this claim is alleged to require an *ab initio* method of determining a protein structure from sequence data of the recited protein. The Examiner further alleges that because the step does not allow for generation of structures from data other than sequence data of the recited protein, some embodiments of claims 42 and 46 (drawn to searching protein structure databases or homology modeling) and claims 43 and 47 (drawn to the use of x-ray crystallographic or NMR spectroscopy structural data) are allegedly drawn to subject matter that is independent or distinct from that originally claimed. The Examiner asserts that the originally presented subject matter has been constructively elected by original presentation for prosecution on the merits,

and, as such, claims 43 and 47 are withdrawn from consideration as being directed to a non-elected subject matter per 37 C.F.R. 1.142(b) and MPEP 821.03. Applicant respectfully disagrees.

It is respectfully submitted that contrary to the Examiner's assertion, claims 42 (in part), 43, 46 (in part), and 47 are not drawn to a non-elected matter. The original requirement for restrictions is as follows:

> Group I, including claims 1-19 and 33-37, directed to a method of polymorphism-based drug candidate design, classified in class 702, subclass 27;
>
> Group II, including claims 20-22, directed to a method of polymorphism-based drug therapy selection, classified in class 702, subclass 27;
>
> Group III, including claim 23, directed to a method of polymorphism-based clinical prognosis prediction, classified in class 702, subclass 27;
>
> Group IV, including claim 24, directed to a method of polymorphism-based drug design against drug-resistant targets, classified in class 702, subclass 27;
>
> Group V, including claim 25, directed to a method of identification of compensatory mutations, classified in class 702, subclass 27; and
>
> Group VI, including claims 26-32 and 38-40, directed to a method of making a polymorphism database and computer systems comprising a polymorphism database, classified in class 702, subclass 19.

None of the groups are limited to any method involving generation of 3-D structures solely by *ab initio* methods. Responsive to the requirement for restriction, Group III, claim 23, drawn to a method of polymorphism-based clinical prognosis prediction, was elected. Original claim 23 does not recite that 3-D structures are determined solely by *ab initio* methods; the words *ab initio* do not appear in this claim, nor, as discussed below does the specification support such a limited interpretation of the claims.

The originally elected claim encompasses any method for determining 3-D protein structures.

In the instant application, applicant originally elected Group III, claim 23, drawn to a method of polymorphism-based clinical prognosis prediction, for examination on the merits. Neither originally elected claim 23 nor the claims that were added in the Response dated February 13, 2003, are limited to *ab initio* methods for generating structures of proteins. As such, claims 42 (in part), 43, 46 (in part), and 47 are not adding subject matter that has been withdrawn from consideration and should be examined as part of the elected subject matter.

Original claim 23 is as follows:

23. A computer-based method for predicting clinical responses in patients based on genetic polymorphisms, comprising:

obtaining one or more amino acid sequences for a protein that is the product of a gene exhibiting genetic polymorphisms;

generating 3-D protein structural variant models from the sequences;

building a relational database of protein structural variants derived based on genetic polymorphisms and observed clinical data associated with particular polymorphisms exhibited in the patients, wherein the database comprises:

3-D molecular coordinates for the structural variant-drug complex models;

a molecular graphics interface for 3-D molecular structure visualization;

functionality for protein sequence and structural analysis;

database searching tools; and

observed clinical data associated with the genetic polymorphisms;

obtaining a protein structural variant based on the same gene associated with a polymorphism in a patient;

generating a 3-D protein model based on the subject's gene sequence;

screening/comparing the 3-D model derived from the subject to the structures contained in the database by:

identifying structures in the database that are similar to the model derived from the subject; and

predicting a clinical outcome for the patient based on the clinical data associated with the identified structures.

Hence, original claim 23 is directed to computer-based methods for predicting clinical responses in a patient in which models of structural variant

proteins in patients are generated and compared to structural variant models in a database. Clinical data associated with structural variant models that are similar to the patient's structural variant models are used to predict clinical outcomes for the patient.

Original claim 23 clearly does not include a recitation that the protein structures are generated by *ab initio* methods. Claim 23 is a generic claim that encompasses any method for generating 3-D protein structures from sequences that is consistent with the disclosure of the specification.

As stated in the MPEP 904.01,

> The breadth of the claims in the application should always be carefully noted; that is, the examiner should be fully aware of what the claims do not call for, as well as what they do require. During patent examination, *the claims are given the broadest reasonable interpretation consistent with the specification*. See *In re Morris*, 127 F.ed 1048, 44 USPQ2d 1023 (Fed. Cir. 1997). [emphasis added]

As stated in the MPEP 2111, paragraph 1,

> During patent examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification." Applicant always has the opportunity to amend the claims during prosecution, and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. In re Prater, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-51 (CCPA 1969)

Thus, in view of MPEP 904.01 and MPEP 2111, paragraph 1, claim 23 and claims dependent thereon should be given the broadest reasonable interpretation that is consistent with the specification. Although the specification should not be read into the claims, the teachings of the specification should not be ignored if claims are to be given their broadest reasonable interpretation in light of the specification.

It is respectfully submitted that interpreting the originally elected claim 23 as requiring only *ab initio* methods does not provide this claim its broadest reasonable interpretation, and is not consistent with the specification nor the language of the claim. As discussed in the Response dated February 13, 2003,

the specification does not teach that *ab initio* methods are required to generate 3-D structures of proteins as used in the claimed methods. In particular, the specification in discussing each step of the methods, teaches (see, *e.g.*, pages 13-16) that 3-D protein structures can be generated by a variety of methods, including *ab initio* methods. The specification states (emphasis added):

> *3-D structural models of the native protein or of the protein structural variants are then determined*, either through experimental methods, for example, x-ray crystallography or NMR, from a protein structure database, such as the PDB, or by using any of a number of well known techniques for predicting protein structure from sequence, for example, homology modeling, *de novo* protein folding algorithms and methodologies, and other computational protein structure prediction methods. Homology modeling techniques are among those preferred herein.

Hence it is clear that the step of generating 3-dimensional (3-D) protein structural variant models from the sequences of the polypeptides is not intended to be limited to *ab initio* methods. The claim does not recite that the 3-D protein structural variant models are generated by *ab initio* methods only. In fact, the phrase "generating 3-D protein structural variant models from the sequences" recited in original claim 23 does not refer to *ab initio* methods and, as described in the specification (pages 13-16) is not to be limited to *ab initio* methods. Moreover, the above-referenced phrase does not state that the 3-D protein structural variant models are generated solely "from the sequences" and, hence, should not be interpreted as requiring solely *ab initio* methods.

Thus, based on the language of the claim and the support illustrated in the specification, claim 23, as originally filed, encompasses a variety of methods, including *ab initio* methods, for use in methods as claimed. Therefore, contrary to the Examiner's assertion, the scope of the originally elected claim is generic and does not only encompass *ab initio* methods.

There is nothing in the specification nor original claim 23 that teaches that this step is limited solely to *ab initio* methods and to no other methods. In fact, the specification teaches that *ab initio* methods can be used in combination

with other methods, such as experimental methods and homology modeling, to generate 3-D protein structures (pages 13-16 and the Examples). Thus, this step does allow for generation of structures from data other than sequence data of the recited protein. Therefore, the subject matter of the originally elected claim 23 is not limited solely to *ab initio* methods for generating structures of proteins.

Claims 42 (in part), 43, 46 (in part), and 47 are not drawn to subject matter that is independent and distinct from originally elected claim 23.

As noted above, claim 23 is directed a computer-based method for predicting clinical responses in a patient in which 3-D models of structural variant proteins are generated by a variety of methods, including *ab initio* methods. Accordingly, methods that employ any of the variety of methods described in the specification as encompassed by original claim 23 are not withdrawn from consideration, contrary to the Examiner's assertions.

For example, claims 42, 43, 46, and 47, which are dependent on claim 23, are also directed to a computer-based method for predicting clinical responses in a patient, which is the subject matter of original claim 23.

Claims 42, 43, 46, and 47 are as follows:

42. The method of claim 23, wherein the step of determining 3-D protein structural variant models is performed by a method selected from the group consisting of experimental methods, searching protein structure databases, homology modeling, molecular modeling, de novo protein folding, computational protein structure prediction, *ab initio* methods and combinations thereof.

43. The method of claim 42, wherein the experimental methods include x-ray crystallography and NMR spectroscopy.

46. The method of claim 41, wherein the step of determining 3-D protein structural variant models is performed by a method selected from the group consisting of experimental methods, searching protein structure databases, homology modeling, molecular modeling, de novo protein folding, computational protein structure prediction, *ab initio* methods and combinations thereof.

47. The method of claim 46, wherein the experimental methods include x-ray crystallography and NMR spectroscopy.

Claims 42, 43, 46, and 47 do not recite that 3-D protein structures are determined solely by methods other than *ab initio* methods. Instead, these dependent claims encompass *ab initio* methods and other methods of determining 3-D protein structures. Claims 42, 43, 46, and 47 render it clear that a variety of methods can be used to determine 3-D structures of proteins without altering the scope of the originally elected claim 28. Therefore, contrary to the Examiner's assertions, claims 42, 43, 46, and 47 fall within the purview of the elected subject matter and, thus, do not add subject matter withdrawn from consideration. As such, claims 42 (in part), 43, 46 (in part), and 47 should not be withdrawn from consideration.

THE REJECTION OF CLAIMS 23, 41, 42, 44-46, 48, AND 49 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claim 23, 41, 42, 44-46, 48, and 49 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one of skill in the art to which it pertains, or with which it is most clearly connected, to make and/or use the claimed subject matter for the reasons of record in the Office Action mailed August 13, 2002.

The Examiner asserts that applicant's arguments in the response dated February 13, 2003, are not persuasive. The Examiner contends that applicant states that the specification shows how to determine the structure of a protein by use of x-ray crystallography, NMR, or a protein structure database but that the elected subject matter is limited to *ab initio* methods. The Examiner further contends that applicant points to Example 1 which employs prior crystal structures of target NS3 protease of HCV rather than the allegedly claimed *ab initio* determination of protein structure. The Examiner asserts that applicant points to references, such as Balaji *et al.*, Osguthorpe, Westhead and Thornton, Jones, and Samudrala *et al.*, in the Information Disclosure Statement filed February 13, 2003, for support of enablement but that these references do not

provide enablement. The Examiner maintains that Figure 2 of Sternberg *et al.* and Table 1 of Koehl *et al.* show poor performance [of protein structure prediction] when no structural data is available. Finally, in response to applicant's argument that accurate prediction of structure is not required to use the method, the Examiner contends that it is not clear how such comparison can be made if the predicted structures are inaccurate. This rejection is respectfully traversed.

Summary of arguments below:

1) The scope of the claims is commensurate with the scope of enablement provided to one skilled in the art by the disclosure in the instant application; 2) the claims recite that the 3-D structures are determined for the polymorphic proteins (proteins that are the product of a gene exhibiting polymorphisms); such determination can be effected by any of a variety of methods, including *ab initio* methods for determining 3-D structures of polymorphic proteins; and 3) there is no evidence of record that establishes that *ab initio* methods cannot be used to effect the requisite comparison between and among the structures of polymorphic protein variants.

The references, such as Balaji *et al.*, Osguthorpe, Westhead and Thornton, Jones, and Samudrala *et al.*, in the Information Disclosure Statement filed February 13, 2003, are not provided for support of enablement but to counter the Examiner's contention that *ab initio* methods are inoperative. These references demonstrate that for purposes of comparison between and among 3-D structures of similar proteins, *ab initio* methods are effective.

RELEVANT LAW

To satisfy the enablement requirement of 35 U.S.C § 112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. *Atlas Powder Co. v. E.I. DuPont de Nemours*, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be satisfied by providing sufficient disclosure, either through illustrative examples

or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything *within the scope* of a broad claim." *In re Anderson*, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of 35 U.S.C. §112, first paragraph "can be fulfilled by the use of illustrative examples **or** by broad terminology." *In re Marzocchi et al.*, 469 USPQ 367 (CCPA 1971)(emphasis added).

The inquiry with respect to scope of enablement under 35 U.S.C. § 112, first paragraph, is whether it would require **undue** experimentation to make and use the subject matter as claimed. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims (i.e. the "Forman factors"). *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

PTO GUIDELINES

The standard for determining whether the specification meets the enablement requirement is whether it enables any person skilled in the art to make and use the claimed subject matter without **undue** experimentation. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400 (Fed. Cir. 1999) (emphasis added). In determining whether any experimentation is "undue," the above-noted factors are to be considered.

As instructed in the published PTO guidelines, it is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The analysis must consider all the evidence related to each of the factors, and any conclusion of non-

enablement must be based on the evidence as a whole. *Id.* 8 USPQ2d at 1404 & 1407.

The starting point in an evaluation of whether the enablement requirement is satisfied is an analysis of each claim to determine its scope. As set forth in the guidelines, all questions of enablement are evaluated against **the claimed subject matter**. The focus of the inquiry is whether everything within the scope of the claim is enabled. With respect scope of enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. *In re Moore*, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971). Once the scope of the claims is addressed, a determination must be made as to whether one skilled in the art is enabled to make and use the entire scope of the claimed subject matter without undue experimentation. The rejection is not valid. It is alleged that claims 23, 41, 42, 44-46, 48, and 49 contain subject matter that is not enabled in the specification. To the extent that this rejection applies to claims 43 and 47, claims 43 and 47 are addressed in the arguments as well.

Analysis

As noted above, the claims must be properly construed in order to perform an enablement analysis as mandated by the PTO guidelines and caselaw. Because the Examiner has <u>improperly construed</u> the claims as requiring solely *ab initio* methods for generating 3-D structures of polymorphic proteins, it is respectfully submitted that the rejection of the instant claims as not being enabled by the specification <u>cannot be valid</u> since the basis for the rejection is improper.

Improper characterization of subject matter

As noted above, the subject matter of originally elected claim 23 is a computer-based method for predicting clinical responses in a patient in which models of structural variant proteins in patients are generated based on the

polypeptide sequences and compared to structural variant models in a database. Clinical data associated with structural variant models that are similar to the patient's structural variant models are used to predict clinical outcomes for the patient. Contrary to the Examiner's allegation that originally elected claim 23 is limited to *ab initio* methods for generating 3-D structures of proteins, original claim 23, when given its broadest interpretation in view of the specification per MPEP 904.01 and MPEP 2111, paragraph 1, is not so limited. Although the specification should not be read into the claims, the teachings of the specification should not be ignored if claims are to be given their broadest reasonable interpretation in light of the specification. As noted above, originally elected claim 23 encompasses a variety of methods for generating 3-D structures. As such, the Examiner's characterization of the originally elected subject matter is improper.

Claim 23 does not require *ab initio* methods for determining 3-D structures of proteins that are the product of a gene exhibiting polymorphisms. As noted above, the specification provides clear basis for this interpretation and amendment, see *e.g.*, page 12, *et seq.:*

> **1. Generating 3-D protein structural variant models**
>
> The first step in the methods provided herein is to obtain patient samples of a gene that exhibits genetic polymorphisms or of a therapeutic target protein derived therefrom. Starting with gene sequences that include single or multiple nucleotide polymorphisms, the amino acid sequences of the translated proteins can be determined. Alternatively, patient samples of the target protein can be obtained and sequenced directly. Multiple sequence analyses can be performed to determine the exact amino acid variations or mutations resulting from the genetic polymorphisms. Numerous methods for identifying genes that encode polymorphisms are known, and numerous polymorphisms have been identified and mapped, and databases of such polymorphisms are publicly available.
>
> 3-D structural models of the native protein or of the protein structural variants are then determined, either through experimental methods, for example, x-ray crystallography or NMR, from a protein structure database, such as the PDB, or by using any of a number of well known techniques for predicting protein structure from sequence, for

> example, homology modeling, *de novo* protein folding algorithms and methodologies, and other computational protein structure prediction methods. Homology modeling techniques are among those preferred herein.

In addition, there is an entire section that describes methods for determining protein structures (see, *e.g.*, Section A1; page 11 *et seq*):

> 3-D structural models of the native protein or of the protein structural variants are then determined, either through experimental methods, for example, x-ray crystallography or NMR, from a protein structure database, such as the PDB, or by using any of a number of well known techniques for predicting protein structure from sequence, for example, homology modeling, *de novo* protein folding algorithms and methodologies, and other computational protein structure prediction methods.

Furthermore, the specification describes a method for generating 3-D structures from primary sequences and related protein structures at page 16:

> A preferred method for generating and refining the structural variant models is illustrated in **FIG. 1**. First, protein sequence information is derived based on the genetic polymorphisms. The subject protein is then assigned to a protein superfamily in order to identify related proteins to be used as templates to construct a 3-D model of the protein. If the superfamily is not known, sequence analysis or structural similarity searched can be performed to identify related proteins for use as templates in homology modeling studies. Once the conserved regions of the model are assembled, *ab initio* loop prediction or *ab initio* secondary structure generation techniques can be used to complete the model. Energetic refinement of the structure can be accomplished by performing molecular mechanics calculations, for example, using an ECEPP type forcefield or through molecular dynamics simulations, for example, using a modified AMBER type forcefield. If necessary, the structures can be dynamically refined, for example, by using a simulated annealing protocol (e.g., 100 ps equilibration, 500 ps dynamics, up to 1000°K, 1 fs data collection). For quality control, the protein structural characteristics, for example, stereochemistry e.g., phi/psi and side chain angles), energetics (e.g., strain energy), packing profile (e.g., packing factor per residue) and hydrophobic packing are evaluated and required to meet acceptable criteria before the structures are used in further studies or input into a structural polymorphism database.

Hence it is clear from the specification, including portions noted above, that structure can be generated by any method known to those of skill in the art.

Therefore, the Examiner's characterization of the claimed subject matter as requiring *ab initio* methods is improper.

Enablement

Notwithstanding the impropriety of the rejection of the instant claims, the instant claims satisfy the enablement requirement of 35 U.S.C. § 112. Application of the above-referenced Wands factors, demonstrates that it would not require undue experimentation for one of skill in the art to practice the methods as claimed.

1. The Breadth of the claims

Claim 23 is as follows:

23. A computer-based method for predicting clinical responses in patients based on genetic polymorphisms, comprising:
identifying proteins that are the products of a gene exhibiting genetic polymorphisms;
obtaining amino acid sequences of the proteins that are the products of a gene exhibiting genetic polymorphisms;
determining 3-dimensional (3-D) protein structural variant models for the proteins that are the product of a gene exhibiting genetic polymorphisms;
building a relational database of protein structural variants based on genetic polymorphisms and observed clinical data associated with particular polymorphisms exhibited in the patients, wherein the database comprises:
3-D molecular coordinates for structural variant-drug complex models; and
observed clinical data associated with the genetic polymorphisms;
obtaining a protein structural variant encoded by a gene exhibiting genetic polymorphisms in a patient;
determining a 3-D protein model based on the patient's gene sequence of a protein exhibiting polymorphisms;
screening or comparing the 3-D model of the protein from the patient to the structures contained in the database by:
identifying structures in the database that are similar to the model derived from the patient's protein; and
predicting a clinical outcome for the patient based on the clinical data associated with the identified structures.

Claims 41-49 are dependent upon claim 23.

Claim 50 is directed to a computer-based method of predicting clinical responses in patients based on genetic polymorphisms by:

> determining a 3-D protein model based on a patient's gene sequence of a gene that exhibits polymorphisms;
>
> screening or comparing the 3-D model of the protein from the patient to the 3-D structures contained in a database of 3-D protein structures by:
>
> identifying structures in the database that are similar to the model of the protein derived from the patient; and
>
> predicting a clinical outcome for the patient based on the clinical data associated with the identified structures.

Claims 51-53 are dependent on claim 50.

As discussed above, the specification teaches that the 3-D protein structures that are used in the claimed methods can be determined by a variety of methods, including *ab initio* methods (pages 13-16 of the specification). Thus, claim 23 encompasses a variety of methods, including, but not limited to *ab initio* methods, and combinations of methods, for determining the 3-D structures of proteins that are used in the claimed methods. Claims 41-49 are dependent on claim 23 and describe a variety of ways of determining the 3-D protein structures that are used in the claimed methods. Like claim 23, claim 50 is directed to computer-based methods of predicting clinical responses in patients and encompasses a variety of methods for determining the 3-D structures of proteins that are used in the methods. Claims 51-53 are dependent on claim 50 and describe a variety of ways of determining the 3-D protein models that are used in the claimed methods.

2. The amount of direction and guidance presented, teachings of the specification

The specification provides guidance for each step of the claimed method, including the variety of ways of determining 3-D structures of proteins. For example, the specification teaches that proteins are identified as the product of a gene exhibiting genetic polymorphisms (pages 2-3). The specification teaches how to obtain one or more amino acid sequences for a protein that is the

product of a gene exhibiting genetic polymorphisms (See *e.g.* page 12, line 21, to page 13, line 2). The specification further teaches that genes exhibiting polymorphisms can be obtained, for example, from patients or from publicly available databases and teaches that the amino acid sequences of the protein product of the genes exhibiting polymorphisms can be determined by, for example, sequencing methods (See e.g. page 12, line 21, to page 13, line 2).

The specification also teaches how to build a relational database of protein structural variants and of observed clinical data associated with the genetic polymorphisms, wherein the database contains 3-D molecular coordinates for structural variant-drug complex models and observed clinical data associated with the genetic polymorphisms (See e.g. page 16, line 25, to page 19, line 30, of the specification). The specification further teaches how to provide the database with a molecular graphics interface for 3-D molecular structure visualization, with tools for protein sequence and structural analysis, and with searching tools (See e.g. page 17, lines 1-28 and page 18, line 27, to page 19, line 5 of the specification).

The specification teaches screening or comparison of the 3-D model derived from the patient to the structures contained in the database by identifying structures in the database that are similar to the model derived from the patient and predicting a clinical outcome for the patient based on the clinical data associated with the identified structures (See e.g. page 3, lines 4-5, page 5, lines 15-29, and page 20 lines 17-21 of the specification). The specification teaches that a variety of methods can be used to determine 3-D structures of proteins, as discussed below.

3-D protein structure determination

The specification provides a variety of methods for determining 3-D protein structural variant models

The specification teaches a variety of ways to determine 3-D protein structural variant models (See e.g. page 12, line 20, to page 16, line 24). The step of "3-dimensional (3-D) protein structural variant models" in claim 23

includes any method by which such model can be constructed. For example, the specification teaches that 3-D protein structural variant models can be determined from "experimental methods, for example, x-ray crystallography or NMR, from a protein structure database, such as the PDB, or by using any of a number of well known techniques for predicting protein structure from sequence, for example, homology modeling, *de novo* protein folding algorithms and methodologies, and other computational protein structure prediction methods" (page 13, lines 3-11).

Homology Modeling

The specification teaches that one of skill in the art can determine 3-D protein structural variant models by, for example, homology modeling in which proteins of unknown structure can be constructed using composite parts of related proteins with known structures (i.e. reference proteins; page 13, lines 16-21). The non-conserved regions of the protein of unknown structure can be constructed using, for example, database searching to identify other proteins with similar variable regions (page 14, lines 26-29). Sequence homology studies can be carried out using sequence alignment algorithms well known in the art (page 14, lines 6-7 and page 15, lines 5-7). Homology modeling can be used in conjunction with *ab initio* loop prediction or *ab initio* secondary structure prediction methods (Figures 2-3 and page 16, lines 3-24 of the specification) or conjunction with the *ab initio* methods described below to determine 3-D protein structures. Thus, the specification teaches a skilled artisan how to determine 3-D protein structure via homology modeling.

***Ab Initio* Methods**

Furthermore, contrary to statements in the Office Action, *ab initio* methods can be used to determine 3-D protein structures, and such methods were known before the effective filing date of the application. For example, the specification teaches that *ab initio* methods, such as those taught in U.S. Patent Nos. 5,331,573; 5,579,250; and 5,612,895, cited on page 15, lines 8-13, of

the instant application and incorporated by reference into the instant application can be used to determine 3-D protein structures. The specification teaches that these methods involve simulating a real-size primary structure of a polypeptide in a solvent box, i.e., an aqueous environment; shrinking the size of the peptide isobarically and isothermally; and expanding the peptide to its real size in selected time periods, while measuring the energy state and coordinates, i.e., the bonds, angles and torsions of the expanding molecule (page 15, lines 13-18). The specification teaches that as the peptide expands to its full size, it assumes a stable tertiary structure and that, in most cases, this tertiary structure will be either the most probable structure (i.e., it will represent a global minimum for the structure) or one of the most probable structures (page 15, lines 18-22). The specification also teaches that once a model it built, it can be refined using energy minimization or molecular dynamics calculations (page 15, line 26, to page 16, line 2).

These methods for *ab initio* determination of 3-D structures are disclosed and claimed in the above-noted patents. For example, U.S. Patent Nos. 5,331,573, 5,579,250 and 5,612,895 each to Balaji *et al.* describe and claim methods of rational drug design that include simulating polypeptides in a way that predicts the most probable secondary and/or tertiary structures of polypeptides without any presumptions as to the conformation of the underlying primary or secondary structure (*i.e., ab initio* methods). These references demonstrate that *ab initio* methods were available at the effective time of filing of the instant application and are included in the instant application as exemplary of *ab initio* methods that can be used.

In particular, the *ab initio* methods of Balaji *et al.* include the steps of (a) simulating a real-size primary structure of a polypeptide of interest in a solvent box (e.g., in an aqueous environment); (b) shrinking the size of the peptide isobarically and isothermally; and (c) expanding the peptide to and beyond its real size in selected time periods, while measuring the energy state and

coordinates, e.g., the ϕ, ψ angles, of the expanding molecule(s). As the peptide expands to its full size and beyond, it assumes a stable tertiary structure that is the most probable structure or one of the most probable structures.

Balaji plots are used to analyze protein structure conformations. The Balaji plots can be generated from data gathered while performing the *ab initio* calculations or can be obtained from other sources. These data include the ϕ, ψ angles for each residue of the peptide as it expands to and beyond its normal size. The Balaji plot is used for: (a) identifying the relative proportional residence time adopted by a particular tertiary structure of a simulated peptide or peptidomimetic; (b) determining sequences or areas of flexibility and rigidness in such peptides or peptidomimetics; and (c) providing instructions and/or insight into the manner in which rigid, constrained or flexible peptide analogs should be modeled, e.g., by computer generation.

Once the most probable conformation of the polypeptide of interest is selected, analogs are designed and synthesized and evaluated for bioactivity. Additionally, peptidomimetics based on the conformation of the synthesized analogs are designed. Thus, the 3-D protein models determined by the Balaji *et al. ab initio* methods are useful in drug design methods.

As described previously, the Balaji *et al. ab initio* methods were successfully used to predict the 3-D structures of endothelin-1 and to design bioactive analogs thereof (U.S. Patent No. 5,736,509). In particular, the drug design methods include the steps of (a) simulating the most probable conformations of endothelin-1 and selecting the most probable conformation from among the simulated conformations; (b) designing and synthesizing cyclic peptides that mimic selected surface features of the three-dimensional structure of endothelin-1; and (c) evaluating the bioactivity of the cyclic peptides (U.S. Patent No. 5,736,509). The cyclic peptides disclosed in U.S. Patent No. 5,736,509 mimic the surface of endothelin-1 and act as **antagonists and otherwise modulate the activity of endothelin**. Thus, the Balaji *ab initio* methods

ar adequate for determining 3-D polypeptide structures for the design of bioactive molecules and drug analogs.

Combination of methods

The specification teaches that combinations of methods can be used to determine 3-D protein structural variant models.

Combination of Homology Modeling and *ab initio* methods

The specification also teaches that a combination of homology modeling and *ab initio* methods can be used to determine structural variant models (page 16, lines 3-24). In particular, protein sequence information that is derived based on the genetic polymorphisms is used to assign the protein to a protein superfamily in order to identify related proteins to be used as templates to construct a 3-D model of the protein. If the superfamily is not known, sequence analysis or structural similarity searched can be performed to identify related proteins for use as templates in homology modeling studies. *Ab initio* loop prediction or *ab initio* secondary structure generation techniques are then used to complete the model (as shown in Figures 1-3). The structural variant model can be energetically refined by performing molecular mechanics calculations, for example, using an ECEPP type force field or through molecular dynamics simulations, for example, using a modified AMBER type force field. If necessary, the structures can be dynamically refined, for example, by using a simulated annealing protocol (e.g., 100 ps equilibration, 500 ps dynamics, up to 1000°K, 1 fs data collection). For quality control, the protein structural characteristics, for example, stereochemistry e.g., phi/psi and side chain angles), energetics (e.g., strain energy), packing profile (e.g., packing factor per residue) and hydrophobic packing are evaluated and required to meet acceptable criteria before the structures are used in further studies or input into a structural polymorphism database. A protocol for determining 3-D protein structures by using a combination of *ab initio* methods and homology modeling is set forth in Figure 1.

X-ray crystallographic data and molecular modeling

The specification provides working examples of how to determine 3-D protein structure using x-ray crystallographic data and molecular modeling. In Example 1, the structure of NS3-peptide complexes is determined using sequence data in conjunction with crystallographic data of NS3/NS4A peptides and molecular modeling using Monte Carlo simulations and ECEPP/3 force field. Thus, the specification teaches a skilled artisan how to determine 3-D protein structure via x-ray crystallographic data and molecular modeling.

Therefore, as taught in the specification, the step of "determining 3-D protein structural variant models" in claim 23 can be done by a variety of methods including experimental methods (e.g., x-ray crystallography and NMR), from a protein structure database (e.g.the PDB), homology modeling, *de novo* protein folding algorithms and methodologies, other *ab initio* methods, and other computational protein structure prediction methods, and combinations thereof.

3. Presence of working examples

The specification provides working examples of determining 3-D structural variant models. In Example 1, 3-D models of mutant forms of HCV protease with different inhibitors are determined and used to assess binding correlations between experimental results and computational results. In particular, binding correlations of NS3/NS4A-peptide complexes with two peptide inhibitors were studied and used to validate the 3-D models of the NS3/NS4A-peptide complexes. The binding studies were conducted *in silico* and compared to the experimental results of Ingallinella *et al.* ((1998) *Biochemistry 37*:8906-891.

Determination of 3-D structure of NS3/NS4A-peptide complex

The crystal structure of NS3/NS4A was regularized using molecular mechanics. Peptides were placed into the NS3 binding site by analogy with other serine proteases.

Monte Carlo (MC) simulations were performed on the NS3/NS4A-peptide complexes using ECEPP/3 force field. The sampling method was a biased

probability Monte Carlo with random change of one variable at a time. A Metropolis acceptance criterion was applied after energy minimization (quasi-Newton, up to 1000 steps). Simulations were performed at a temperature of 1000° K. In the peptide, translation/rotation and all torsions were included in the simulation. Protein side-chain χ angles of residues that have at least one atom within 7.0 Å of any atom of the peptide were included. The energy function used in the MC simulations included ECEPP/3 terms for energy *in vacuo* (VDW, H-bond, electrostatic and torsion potentials); distance dependent electrostatics with e = 4.0; and surface energy with atomic solvation parameters. The total energies of the complexes were calculated including contributions from: ECEPP/3 VDW, H-bond, S-S bond and torsion terms; exact-boundary electrostatic energy with e=8.0; and side-chain entropies. Hydrophobic free energies were estimated as sA, where A is accessible surface area and s is a tension constant of 0.03 kcal/molÅ^2.

The Monte Carlo (MC) simulations of the NS3/NS4A-peptide complexes were performed with multiple, relatively short MC runs (2000-5000 generated structures). New docking cycles were started from the lowest-energy or other interesting structures found in previous runs. Structures saved during various MC runs were sorted by total energies and RMSD, and compressed into a cumulative conformational stack.

Binding energies were calculated for representative structures of each complex thus obtained using the equation:

$$E_{bind} = E_o + E_{compl} - E_{pept} - E_{prot},$$

where E_{compl} is the energy of the NS3/NS4A-peptide complex, E_{pept} & E_{prot} are separate energies of the peptide and NS3/NS4A protein, respectively, and E_o is an adjustable constant.

The binding energy function included: exact-boundary electrostatic contributions; side-chain entropy; and surface tension hydrophobic terms. ECEPP/3 hydrogen-bonding terms were included with a weight of 0.5.

In the model validation studies, modifications were made to the NS3/NS4A-peptide complex models, and the binding energies of the modified complexes were correlated with those expected from experimental IC_{50} values. Changes in calculated binding energies upon modifications, ΔE_{bind} (calc), were compared to the values expected from ratios of inhibitory potencies, ΔE_{bind}(exp).

$$\Delta E_{bind}(exp) = RT\ ln(IC_{50}^{mod}/IC_{50}^{o}),$$

where IC_{50}^{o} and IC_{50}^{mod} are inhibitory potencies of the parent and modified compounds.

The correlation between experimental and calculated changes in binding energy upon ligand modifications in the binding site of NS3 is shown in **FIG. 4.**

The models were in agreement with SAR data for peptide inhibitors of NS3. Predicted changes in binding energy upon modification of the protein and peptides correlate reasonably well with the changes expected from IC_{50} ratios. For example, standard deviations of ΔE_{bind}(calc) - ΔE_{bind}(exp) were 0.8 and 1.6 kcal/mol for Models 1 and 2, respectively, with correlation coefficients of 0.62. After the largest outlier was removed from each dataset, correlations improved to 0.81 and 0.76, respectively.

Thus, the fact that the *in silico* studies correlate well with experimental data validates the structure models determined by the methods described above for use in structure-based drug design methods and other methods claimed in the instant application. Moreover, the correlation of the computational data with experimental data demonstrates that the skilled artisan can use the protocols taught in Example 1 to determine 3-D structural variant models.

4. Nature of the claimed subject matter

The claimed subject matter is directed to the prediction of clinical responses of patients by comparing 3-D protein structures of structural variants encoded by genes exhibiting polymorphisms to 3-D protein structural variant models in relational databases. Clinical data associated with structural variant models that are similar to the patients' structural variant models are used to

predict clinical outcomes for the patient. As taught in the specification, clinical information that can be used to predict responses in patients includes, but is not limited to, patients receiving a specific treatment regimen or exhibiting a particular clinical response to a given drug or the duration of a particular drug treatment (page 5, lines 1-4). Moreover, the protein structural variant models that are used in the comparison of patient data can be determined by experimental methods (e.g. x-ray crystallography or NMR), from a protein structure database, (e.g. PDB), homology modeling, *de novo* protein folding algorithms, other *ab initio* methods, computational protein structure prediction methods, and combinations thereof. As disclosed in the instant specification and as discussed below, these methods of determining protein structures are well known in the art.

5. Level of skill

The level of skill in this art of polypeptide structure and modeling is recognized to be high. For example, the numerous articles and patents that are of record in this application that are authored by those of a high level of skill for an audience of a high level of skill further evidences the high level of skill in this art. For example, Balaji disclose *ab initio* methods that can be used to determine polypeptide structures (U.S. Patent Nos. 5,331,573; 5,579,250; and 5,612,895). Dudek *et al.* discloses *ab initio* loop predictions and molecular modeling that can be used to determine polypeptide structures (J. Comp. Chem. (1998) 19:548-573). Balasubramanian discloses Ramachandran plots that can be used to determine polypeptide structures (Nature (1974) 266:856-857). Weiner and Ramnarayan disclose molecular modeling that can be used to determine polypeptide structures (J. Comp. Chem. (1986) 7:230-252; J. Chem. Phys. (1990) 92:7057-7076). Nanni *et al.* and Kroeger *et al.* disclose 3-D protein structures of HIV reverse transcriptase and protease (*Perspectives in Drug Discovery and Design 1*:129-150 (1993); *Protein Eng. 10*:1379-1383 (1997)). Love *et al.* and Yan *et al.* disclose the crystal structure of NS3 protein

without the NS4A cofactor (*Cell 87*:331-342 (1996) and *Protein Sci.* 7:837-847 (1998)).

6. State of the prior art:

At the time of the effective filing date of this application and before, the skilled artisan knew various methods of determining 3-D structures of proteins from sequence data. Further, there is a large body of literature directed to determining 3-D structures of proteins from experimental and computer-based methods, and combinations thereof.

The articles cited in the specification, of record in this application, describe various methods of determining 3-D protein structures. The following represents some exemplary articles that evidence the knowledge of those of skill in the art at the time of filing of the instant application:

Balaji *et al.*, "Method of Rational Drug Design Based on Ab Initio Computer Simulation of Conformational Features of Peptides," U.S. Patent No. 5,612, 895 (March 18, 1997), which describes *ab initio* prediction of the tertiary structure of polypeptides without any presumption as to the conformation of the underlying primary or secondary structure, as noted above. The Balaji method involves computer simulation of polypeptides by simulating a real-size primary structure in an aqueous environment, shrinking the size of the polypeptide isobarically and isothermally, and expanding the simulated polypeptide to its real size in selected time periods. "Balaji plots" are used to identify those portions of the predicted peptide structure that are most flexible or rigid. The Balaji methods are used to determine polypeptide models that are used to design bioactive drug analogs (See U.S. Patent No. 5,736,509 (April 7, 1998); See also Balaji *et al.* U.S. Patent No. 5,331,573 (July 19, 1994) and U.S. Patent No. 5,579,250 (November 6, 1994));

Dudek *et al.* "Protein Prediction Using a Combination of Sequence Homology and Global Energy Minimization: II. Energy Functions," (1998) J. Comput. Chemistry 19:548-573, which describes the application of *ab initio*

methods using global energy minimization to reconstruct surface loops that were stripped from the protein crystal structures of proteins such as avian pancreatic polypeptide, crambin, bptl, erabutoxin B, immunoglobulin domain, ribonuclease A, and lysozyme. The surface loops that were reconstructed using *ab initio* methods were in good agreement with the protein crystal structure with RMSD < 1 with a weighting factor of 1 (Table IX).

Abagyan and Totrov, "Ab Initio Folding of Peptides by the Optimal-Bias Monte Carlo Minimization Procedure," (May 1, 1999) 151:402-421, which describes the structure prediction of BBA5 protein-like folded peptide using *ab initio* methods employing a Monte Carlo minimization-based global optimization algorithm (i.e. OBPMC) in conjunction with a set of biased random moves. Using the OBPMC method, Abagyan and Totrov generated low energy conformations of the BBA5 protein and compared it to the experimental structure of BBA1 (an analog of BBA5 with the synthetic residue Fen at the 3 position) and observed similarity between the *ab initio* generated structure and the experimental structure of the analog (i.e. RMSD 3.8).

Osguthorpe, "Improved Ab Initio Predictions with a Simplified, Flexible Geometry Model," Proteins: Structure, Function, and Genetics Suppl 3 (November 8, 1999) 186-193, which describes the *ab initio* prediction of the tertiary structure of T56, (a target that was predicted at the CASP3 meeting described by Sternberg *et al.* and Koehl *et al.*) and which demonstrates that for new folds, *ab initio* methods are as good as other methods in getting an approximation to the native structure;

Westhead and Thornton "Protein structure prediction," Curr Opin in Biotechnology (1998) 9:383-389, which describes improvements in comparative modeling studies;

Eisenhaber *et al.* "Protein structure prediction: recognition of primary, secondary, and tertiary structural features from amino acid sequence," Critical Rev. in Biochem and Mol. Biol. (1995) 30:1-94, which describes prediction of

protein structure from amino acid sequence computational methods, threading methods, sequence alignment methods, and homology modeling;

Jones, "Successful *ab initio* prediction of the tertiary structure of NK-Lysin using multiple sequences and recognized supersecondary structural motifs," Proteins: Structure, function, and Genetics, Suppl 1 (1997) 185-191, which describes tertiary protein structure prediction based on the assembly of recognized structural fragments taken from highly resolved protein structures;

Samudrala *et al.*, "Ab initio protein structure prediction using a combined hierarchical approach," Proteins: Structure, function, and Genetics Suppl 3 (November 8, 1999) 194-198, which describes the prediction of 3-D structures for 13 proteins using lattice based scoring function in conjunction with distance geometry methods;

Dunbrack *et al.* "Meeting review: the Second Meeting on the Critical Assessment of Techniques for Protein Structure Prediction (CASP2), Asilomar, California, December 13-16, 1996," Folding and Design (1997) R27-R42, which reviews the comparative modelling, fold recognition, and *ab initio* structure prediction presented at CASP2; and

de Dios *et al.* "Secondary and Tertiary Structural Effects on Protein NMR Chemical Shifts: An ab Initio Approach," Science (1993) 260:1491-1496, which describes the use of NMR to refine protein structures;

These articles and patents are representative of the numerous ways to determine 3-D protein structures. The articles range from pure experimental methods (such as NMR spectroscopy) to pure computational methods (such as *ab initio* methods of Balaji *et al.*). Therefore, the knowledge of those of skill in the art is extensive and methods for determining 3-D protein structures is well known.

7. Predictability

As is known to those of skill in the art (described above), the level of knowledge and skill in the determination of 3-D protein structures is so high that

as of the effective filing date of the instant application, it would not have required undue experimentation by one of skill in the art to determine 3-D protein structures. As noted above, one of skill in the art can use experimental methods (e.g. NMR and x-ray crystallography), computational methods, homology modeling, de novo prediction, *ab initio* methods, or any combination thereof to determine 3-D protein structures.

CONCLUSION

The specification of the instant application teaches a skilled artisan how to determine 3-D protein structures and how to make and use the elements of the claimed methods. In light of the breadth of the claims, the teachings and working examples in the specification, and the high level of skill and extensive knowledge of those in this art, it would not require undue experimentation for a person of skill in the art to determine 3-D protein structures for use in the instant claims and to practice the claimed methods. As disclosed in the specification and in the cited art, the skilled artisan can use experimental methods, computational methods, homology modeling, and/or *ab initio* methods to determine 3-D protein structures. Therefore, the specification is enabling for making and using the full scope of the claimed subject matter.

Rebuttal to comments by the Examiner

The Examiner's arguments are premised on the characterization of the elected subject matter as requiring only *ab initio* methods for determining 3-D structures of proteins. As noted above, this characterization is incorrect, and, as such, the rejections of the instant claims fail. Furthermore, there is no evidence of record to establish that *ab initio* methods alone cannot be used to generate 3-D models. Furthermore, when the claims are properly interpreted to encompassing a variety of methods for determining 3-D protein structures, the issues raised by the Examiner are moot.

The specification

The Examiner asserts that in a Response dated February 13, 2003, applicant states that the specification shows how to determine the structure the structure of a protein by use of x-ray crystallography (e.g. Example 1), NMR, or a protein structure database but that the elected subject matter is limited to *ab initio* methods.

As discussed above, contrary to the Examiner's assertion, the elected subject is not limited to *ab initio* methods. Nowhere in the file history was a requirement for election of a particular method for determining a 3-D protein structure set forth. As noted above in the section entitled "Restrictions," the originally elected subject matter encompasses any method of determining 3-D structures of proteins, including, but certainly not limited to, *ab initio* methods.

The Response, dated February 13, 2003 and the instant response demonstrate that the specification teaches methods for generating 3-D structures of proteins. There is entire section titled " **1. Generating 3-D protein structural variant models**", and what follows in that section is a description of a variety of methods for determination of 3-D protein structures by x-ray crystallography (e.g. Example 1), NMR, or a protein structure database. In addition to these passages, applicant cites portions of the specification that teach that 3-D structures of proteins can be determined by other methods, such as homology modeling, *de novo* protein folding algorithms and methodologies, other computational protein structure prediction methods, *ab initio* methods, a combination of x-ray crystallography and *ab initio* methods, and a combination of homology modeling and *ab initio* methods (pages 13-16 of specification). Thus, as noted in the Response dated February 13, 2003, and as noted above, the specification clearly shows that the instant claims encompass any method for determination of 3-D structures.

Furthermore, the Examiner has not provided any evidence that *ab initio* methods as described in the specification are not adequate to determine

structures for comparison in accord with the claimed method. As described in the previous response, there are methods that demonstrably work to generate such structures.

References in the Information Disclosure Statement (IDS) dated February 13, 2003

The Examiner alleges that the following references do not support enablement of the claimed subject matter. As pointed out above, the references are not provided to support enablement, but to rebut the Examiner's statement that such methods are inoperative. As discussed in the previous response, these references counter the statements by the Examiner that *ab initio* methods are not operative.

Furthermore, as discussed above, there is nothing in the claims or specification that requires limitation of the claims to methods that employ *ab initio* methods to determine 3-D structures of proteins. There has been no restriction requirement among methods for such determination nor does the specification contemplate a single method. As noted above, the instant claims encompass a variety of methods for determining 3-D structures of proteins.

Balaji *et al.*

The Examiner asserts that Balaji *et al.* (U.S. Patent Nos. 5,331,573; 5,579,250; and 5,612,895) exemplifies *ab initio* prediction of the structure of endothelin, which is a 21 amino acid peptide and peptides that bind endothelin. The Examiner alleges that Balaji *et al.* is not commensurate with the scope of the claims that include proteins.

Balaji *et al.* exemplifies *ab initio* prediction of the structure of polypeptides. Balaji *et al.* does not teach or suggest that the *ab initio* methods cannot be applied to proteins. The Examiner has provided no reasons why the Balaji *ab initio* methods cannot be used to determine 3-D structures of variant models for use in the instantly claimed methods, other than his bare allegation that the methods of Balaji *et al.* are not commensurate with the scope of the

claimed subject matter. Mere allegations do not constitute credible evidence. Furthermore, Balaji *et al.* patents (U.S. Patent Nos. 5,579,250, 5,612,895 and 5,331,573) state that they provide:

> A method of predicting the most probable tertiary structure of a peptide is provided without any presumption regarding the underlying structural characteristics of the peptide. Such method is referred to herein as an "*ab initio*" method, where the term is used to emphasize there are no initial presumptions made as to what form the simulated tertiary structure may ultimately take.

The Examiner in stating that *ab initio* methods are not effective has improperly taken official notice of facts outside the record that are not capable of instant and unquestionable demonstration as being "well-known." As stated in M.P.E.P. § 2144.03:

> "[A]ssertions of technical facts in areas of esoteric technology must always be supported by citation of some reference work" and "allegations concerning specific 'knowledge' of the prior art, which might be peculiar to a particular art should also be supported." Furthermore the applicant must be given the opportunity to challenge the correctness of such assertions and allegations." see In re Ahlert, 424 F.2d 1088, 165 USPQ 418, 420-421 (CCPA 1970).
>
> When a rejection is based on facts within the personal knowledge of the examiner, the data should be stated as specifically as possible, and the facts must be supported, when called for by the applicant, by an affidavit from the examiner. Such an affidavit is subject to contradiction or explanation by the affidavits of the applicant and other persons. See 37 CFR 1.107.

Thus, it is respectfully requested that the Examiner provide a citation of some reference work that indicates that the *ab initio* methods of Balaji et al. cannot be used to determine 3-D structures of proteins.

The Examiner has provided no proof that the methods of Balaji *et al.* cannot be used with the instant claims. Furthermore, the methods claimed in Balaji *et al.* to not limit the size of the polypeptide to which they are applied. Urging that the methods of Balaji *et al.* are inoperative is not appropriate. The

Examiner is reminded that the Office cannot comment on the validity of a patent (MPEP 1701).

Osguthorpe

The Examiner alleges that although Osguthorpe ("Improved Ab Initio Predictions with a Simplified, Flexible Geometry Model," Proteins: Structure, Function, and Genetics Suppl 3 (November 8, 1999) 186-193) shows some success at prediction of secondary protein structure, Osguthorpe points out that "these results also show how even with secondary structure predictions of 60-70%, generating correct tertiary structures requires significant additional information as the overall RMS of these structures ranges from 10 to 19 (excluding T0065)."

Osguthorpe discloses structure prediction for nine targets from the CASP3 meeting and compares them to experimental structures. Osguthorpe discloses that the structure prediction for one target, T0065, was successful with a RMS of 3.8 and a Q3 of 90% (see abstract, page 188, Table I). The passage cited by the Examiner refers to other targets whose structures were not accurately predicted (i.e. excluding the successful T0065 target).

Westhead and Thornton

The Examiner alleges that page 387 of Westhead and Thornton ("Protein structure prediction," Curr Opin in Biotechnology (1998) 9:383-389) states that the quality of models is dependent on comparison to sequences of related sequences with known structures and that when less than 20% of the sequence of interest is similar to a known structure, the modeling algorithms rapidly deteriorate and the inaccuracies are very large.

Westhead and Thornton reviews the progress in structure prediction of proteins by considering three aspects of structure prediction: (1) secondary structure prediction, (2) fold recognition, and (3) homology modeling. In the section entitled "comparative modeling" (page 385), Westhead and Thornton discloses improvements in homology modeling. The passage cited by the

Examiner discloses in the comparative modeling category, the quality of the model is dependent on the sequence alignment and that below 20% sequence identity, the inaccuracies in the models are large. Like Westhead and Thornton, the specification of the instant application teaches that homology modeling (i.e. comparative modeling) can be used to determine 3-D structures.

Jones

The Examiner alleges that page 190 of Jones ("Successful *ab initio* prediction of the tertiary structure of NK-Lysin using multiple sequences and recognized supersecondary structural motifs," Proteins: Structure, function, and Genetics, Suppl 1 (1997) 185-191) states that "the predicted structure was quite a long way from the experimental structure."

Jones discloses tertiary protein structure prediction based on the assembly of recognized structural fragments taken from highly resolved protein structures. The passage cited by the Examiner states that although the overall fold for Nk-lysin protein was correctly predicted, the predicted structure was a long way from the experimental structure. The reference provides some suggestions for improving the model and suggests that an "all atom model with specific interactions" will help produce an accurate prediction of a native protein structure (page 190).

Samudrala *et al.*

The Examiner alleges that Samudrala *et al.* ("Ab initio protein structure prediction using a combined hierarchical approach," Proteins: Structure, function, and Genetics Suppl 3 (November 8, 1999) 194-198) points out in the abstract that less than half of the proteins analyzed had a predictable structure and that Table 1 shows that the level of resolution of the predictions was low.

Samdrala *et al.* discloses prediction of 3-D structures of 13 proteins using a hierarchical approach. The reference discloses that the global topology/shape for all or a large part of 6/13 proteins was predicted. Samdrala *et al.* does not bar the enablement of the instant claims because the specification does not

teach that the methods of determining 3-D structures are limited to *ab initio* methods. In fact, the specification teaches that computational methods, such as *ab initio* methods, can be combined with other computational methods or with experimental methods to determine 3-D protein structures, which can increase the accuracy of 3-D structure prediction.

Koehl *et al.* and Sternberg *et al.*

The Examiner alleges that Figure 2 of Sternberg *et al.* (Curr Opin in Struc. Biol. (1999) 9:368-373) and Table 1 of Koehl *et al.* (Nature Struc. Biol. (1999) 6:108-111) show poor performance when no structural data is available.

Sternberg *et al.* and Koehl *et al.* disclose protein structure prediction presented at a CASP3 meeting. According to Koehl *et al.*, in the field of protein structure prediction, the results at CASP "does not test how well other scientists can expect to do, nor how well totally automated methods would do [in the field of protein structure prediction]." As such, references like Sternberg *et al.* and Koehl *et al.*, which describe protein prediction results from CASP, should not be used to measure the state of art of protein structure prediction.

Accuracy of Predictions

The Examiner contends that it is not clear how comparisons of a reference target protein and a variant protein of a patient can be made if the predicted structures are inaccurate. The instant claims are directed to the use of 3-D structures of proteins that are the product of genes exhibiting polymorphisms to predict clinical responses in patients, not to the accurate prediction of 3-D structures. In the instant methods, the 3-D structure of protein derived from a patient is compared to 3-D structures in a relational database; structures that are similar to the 3-D model from the patient are identified; and a clinical outcome for the patient is predicted based on clinical data associated with the identified structure.

Additionally, the Examiner refers to inaccuracies of protein structure prediction in the context of *ab initio* methods. As discussed above, the

specification does not teach that the instant claims are limited *ab initio* methods. In fact, the specification teaches that a variety of methods, including *ab initio* methods can be used to determine 3-D structures of proteins, as discussed above. The specification also teaches that methods, such as *ab initio* methods, can be combined with other methods, such as experimental methods and homology modeling to determine 3-D structures of proteins. Therefore, any inaccuracies in the ab initio prediction of protein structures are irrelevant.

Koehl *et al.* and Samudrala *et al.* indicate that *ab initio* methods can accurately predict the structures of portions of polypeptides; these structures can be used in the instantly claimed methods (the specification states, for example at page 15, that "*ab initio* methods can be used in combination with an existing partial homologous structure to generate unresolved portions of the target structure"). For example, if the portions of the polypeptides that are accurately predicted correspond to parts of the polypeptide that are bioactive (e.g. active site), then these portions of reference polypeptides can be compared to the polypeptides from patients to determine the similarity/differences in these portions and to predict clinical responses in patients.

Also, for example, protein structures determined solely by *ab initio* methods can be validated by comparing data from computational binding studies to data from experimental binding studies, as discussed above. Models that have been validated by this comparison can be used in the instant methods of computer-based drug design as shown in the Examples.

THE REJECTION OF CLAIMS 42 AND 46 UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 42 and 46 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention because the phrases "experimental methods" and "searching protein structure databases, homology modeling" do not render it clear that the claims are directed to the elected

subject matter. The bases for this rejection are discussed in turn below. This rejection is respectfully traversed.

Relevant law

Claims are not read in a vacuum but instead are considered in light of the specification and the general understanding of the skilled artisan. Rosemount Inc. v. Beckman Instruments, Inc., 727 F.2d 1540, 1547, 221 USPQ 1, 7 (Fed. Cir. 1984), Caterpillar Tractor Co. v. Berco, S.P.A., 714 F.2d 1110, 1116, 219 USPQ 185, 188 (Fed. Cir. 1983). When one skilled in the art would understand all of the language in the claims when read in light of the specification, a claim is not indefinite.

There are no requirements for terms to be defined in the claims when one of skill in the art can readily determine the meaning of the term based on the description and definitions provided in the specification. In this respect, an applicant is entitled to be its own lexicographer [see, *e.g.*, MPEP 2111.01 "Applicant may be his or her own lexicographer as long as the meaning assigned to the term is not repugnant to the term's well known usage and utilize terms within the claims that are clear from a reading of the specification. *In re Hill*, 73 USPQ 482 (CCPA 1947)."]. When applicant has provided definitions in the specification, the claims are interpreted in light of such definition.

35 U.S.C. § 112, second paragraph requires only reasonable precision in delineating the bounds of the claimed invention. Claim language is satisfactory if it reasonably apprises those of skill in the art of the bounds of the claimed invention and is as precise as the subject matter permits. *Shatterproof Glass Corp. v. Libby-Owens Ford Col.*, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir.), cert. dismissed, 106 S.Ct. 340 (1985).

The amount of detail required to be included in the claims depends on the particular subject matter and the prior art and is not to be viewed in the abstract, but in conjunction with whether the specification is in compliance with the first paragraph of 35 U.S.C. § 112. If the claims, read in light of the

specification, reasonably apprise those skilled in the art of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more:

> [i]t is not necessary that a claim recite each and every element needed for the practical utilization of the claimed subject matter (*Bendix Corp. v United States*, 600 F.2d 1364, 1369, 220 Ct. Cl. 507, 514, 204 USPQ 617, 621 (1979); See, also, *Carl Zeiss Stiftung v. Renishaw plc*, 20 USPQ2d 1094, 1101).

Claims 42 and 46 are alleged to be indefinite in the recitation of the phrase "experimental methods" in line 3 of claim 42 and line 3 of claim 46 because it is not clear if the claim is limited to the elected invention which allegedly uses *ab initio* methods of structural determination from sequence data. Additionally, claims 42 and 46 are alleged to be indefinite in the recitation of the phrase "searching protein structure databases, homology modeling" because the limitations are allegedly not drawn to the elected invention.

The claims

Claims 42 and 46 are discussed above.

As discussed above in the section entitled "Elections/Restrictions," the originally elected subject matter is a computer-based method of predicting clinical responses in a patient in which 3-D structures of structural variant proteins are determined by a variety of methods, not only *ab initio* methods. As also discussed above, *ab initio* methods can be combined with other methods to determine the 3-D structures of proteins for use in the claimed methods.

As such, claims 42 and 46, which are directed to a computer-based method of predicting clinical responses in a patient in which a variety of methods are used to determine 3-D structures of proteins, including, but not limited to, "experimental methods" and ""searching protein structure databases, homology modeling" are within the purview of the originally elected subject

matter. Therefore, the rejection of claims 42 and 46 for failing to point out and distinctly claim the subject matter and for not being drawn to the elected invention fails.

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Respectfully submitted,
HELLER EHRMAN WHITE & McAULIFFE LLP

By: _____
Stephanie L. Seidman, Reg. No. 33,779

Attorney Docket No. 24737-1906B
Address all correspondence to:
Stephanie L. Seidman, Esq.
HELLER EHRMAN WHITE & McAULIFFE
4350 La Jolla Village Drive, 7th Floor
San Diego, California 92122-1246
Telephone: 858 450-8400
Facsimile: 858 587-5360
email:sseidman@HEWM.com